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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/384,959	08/27/1999	RAM SASISEKHARAN	M0656/7046HC	8533

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HELEN C LOCKHART  
WOLF GREENFIELD & SACKS  
600 ATLANTIC AVENUE  
BOSTON, MA 02210

EXAMINER

HUTSON, RICHARD G

ART UNIT PAPER NUMBER

1652

19

DATE MAILED: 06/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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FINAL

**Office Action Summary**

Application No.

09/384,959

Applicant(s)

SASISEKHARAN ET AL.

Examiner

Richard G Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 25 March 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 30-34 and 46-49 is/are pending in the application.
- 4a) Of the above claim(s) 32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 30,31,33,34 and 46-48 is/are rejected.
- 7) ☐ Claim(s) 49 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Applicants amendment of claim 30, 33 and 46 and cancellation of claims 1-29, 35-45 and 50-57, Paper No. 17, 3/25/2002, is acknowledged.

Claims 30-34, and 46-49 are at issue and are present for examination.

Claim 32 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicants comments with respect to claim 32 are acknowledged.

### ***Claim Objections***

Claims 30, 46 and 49 are objected to because of the following informalities: Claims 30 and 46 each are drawn to a method of using a heparinase selected from a number of different heparinases. The format that the claims appear in is confusing and unclear. It is suggested that in order to make the claims clearer, the "colon" after "comprising" be moved to after "any one of".

Claim 49 is dependent on rejected claim 46.

Appropriate correction is required.

### ***Information Disclosure Statement***

Applicants statements regarding the filing of related applications 09/802,285, 09/951,138 and 09/982,548, by common inventors is acknowledged and these applications have been considered as they are relevant to the instant invention.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 33, 34, 46, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection is stated in the previous office action.

Applicants appear to traverse this rejection together with the 112 1<sup>st</sup> paragraph-scope of enablement rejection below. Applicants are reminded that these are two different rejections based on different legal principles. Applicants response as far as it is relevant to this written description rejection will be addressed here.

Applicants traversal as relevant to this written description rejection is on the basis that applicants specification adequately and extensively describes the structure of the heparinases through the description of catalytic and binding sites as well as the relationship of these structures to the function of the enzyme, including working examples demonstrating various mutations which alter the level of enzymatic activity but do not destroy catalytic activity. Applicants further submit that the written description of a claimed genus can be satisfied by the actual reduction to practise or by disclosure of identifying relevant, characteristics and that applicants showed the essential amino acid

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residues within heparinase II responsible for the binding and catalytic function.

Applicants argument further comprises detailed structural information of modifications that applicants have made to the disclosed heparinase II (SEQ ID NO: 2) protein.

Applicants argument is not found persuasive, because while applicants have identified certain amino acid residues important in the catalytic and binding activity of heparinase II, this information in combination with the limited number of described species is insufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. Applicant is reminded that the claimed heparinase variants include all modified heparinase enzymes and that the claimed variants are only limited functionally (i.e. having heparinase activity and a modified product profile that is at least 10% different than a native product profile of a native heparinase II or that has a modified heparinase II  $k_{cat}$  value at least 10% different than a native heparinase II  $k_{cat}$  value). The rejected claims place absolutely no structural limitations on the claimed variants, hence as discussed previously in the 102 rejections the claimed methods read on methods of using heparinase I and heparinase III, as they meet the necessary functional limitations of the rejected claims. While applicants submit that the specification provides adequate structural information about heparinases as they relate to the functional role of the various regions of the enzyme as well as enzyme mutants, applicants claims are not limited in any way to those structural limitations.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

Claims 30, 33, 34, 46, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with a modified heparinase II comprising SEQ ID NO: 2 with a specific substitution at histidine 440 or cysteine 348, does not reasonably provide enablement for those methods of cleaving a heparin-like or heparan sulfate-like glycosaminoglycan comprising contacting said heparin-like or heparan sulfate-like glycosaminoglycan with any modified heparinase having a modified product profile or heparinase  $k_{cat}$  that is at least 10% different than the native heparinase II. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection is stated in the previous office action.

As discussed above, Applicants appear to traverse this rejection together with the 112 1<sup>st</sup> paragraph-written description rejection above. Applicants are reminded that these are two different rejections based on different legal principles. Applicants response as far as it is relevant to this scope of enablement rejection will be addressed here.

Applicants argue that the rejection under 35 U.S.C. §112, first paragraph is not proper because the specification teaches the structure of the heparinases through the description of catalytic and binding sites as well as the relationship of these structures to the function of the enzyme, including working examples demonstrating various mutations which alter the level of enzymatic activity but do not destroy catalytic activity, and the technology to produce these modified heparinases and assess their enzymatic activity is well within the skill in the art. This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., with only a functional and no structural limitation) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Applicant is reminded that the currently rejected claims have **no structural limitations** and thus the claimed genus of variants is infinitesimally large.

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 30,31, 33, 46 and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by Shriver et al. (Journal of Biological Chemistry 273(17): 10160-10167, April 1998).

The rejection was stated in the previous office action.

In response applicants have filed a declaration under CFR 1.131., effectively removing Yini Hu as a co-author of the Shriver et al. paper. This declaration by itself is not effective in overcoming the rejection because the paper remains "by another". The inventive entity of the instant application includes Dongfang Liu and Ganesh Venkataraman and no explanation as to why they were not also authors of the Shriver et al. paper is presented.

Claims 30, 33, 46 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Su et al. (U.S. Patent No: 5,681,733, filed 6/10/1994).

The rejection is stated in the previous office action.

Applicants traverse this rejection on the basis that the claims are not anticipated because Su et al. does not describe each element of the claimed invention. Applicants



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submit that Su et al. does not disclose the production and/or use of modified heparinases having modified product profile or activity. Applicants submit that while Su et al. suggest that modifications to the primary structure of heparinase could be made, Su et al. does not provide any guidance with respect to the preparation of such modifications. This argument is not found persuasive because while it is admitted that Su et al. does not provide guidance on modifying heparinases, specifically heparinase II, the claimed method is to a method of cleavage of a heparin or heparan sulfate-like glycosaminoglycans using a modified heparinase II that is described only by its functional attributes relative to the native heparinase II, as previously stated, the use of heparinases I and III, which themselves have an modified product profile relative to native heparinase II, in the taught cleavage methods anticipates claims 30, 33, 46 and 47.

Thus claims 30, 33, 46 and 47 remain anticipated by Su et al.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 34 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Su et al. (U.S. Patent No: 5,681,733, filed 6/10/1994) as applied to Claims 30, 33,

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46 and 47 above, and further in view of Langer et al. (U.S. Patent No. 4,373,023, issued 2/8/1983).

The rejection is stated in the previous office action.

Applicants traverse this rejection as the above 102 rejection over Su et al., based on the submission that Su et al. does not teach methods of use of the same class of enzymes as the instant invention. Applicants further submit that Langer et al. also does not describe the modified heparinases of the claimed invention. This argument is not found persuasive because as discussed above, since the claimed methods reference heparinases by only functional properties, and not structural characteristics, and the heparinases taught by Su et al. (i.e. heparinases I and III) meet these "functional limitations" the combination Su et al. and Langer et al. would result in the claimed methods being obvious.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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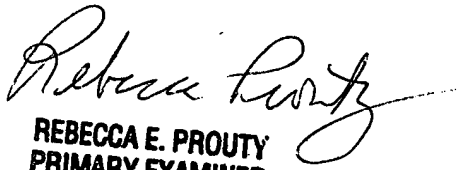
the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.  
Patent Examiner  
Art Unit 1652  
June 21, 2002

  
**REBECCA E. PROUTY**  
**PRIMARY EXAMINER**  
**GROUP 1800**  
1600